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Patents and Growth

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A key aspect of reducing new knowledge to practice in the field of medicine is successfully navigating the process of patenting inventions and licensing them to facilitate their use. University faculty and their departments have much to gain from a detailed understanding of how this is done because even small deviations in laboratory practice, documentation, or execution of the process may completely negate possible benefits. Here we describe good laboratory practice for documentation of medical research, the process of patenting intellectual property, and its potential impact on faculty and their departments. As the field of medicine rapidly changes, faculty and their departments who are knowledgeable about these issues will be best positioned to see their ideas converted into treatments for disease.

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The purpose of medical research is to increase our understanding of the observable world so that discovery can be put into practice to reduce human suffering. Our understanding of skin biology and related medical science has advanced greatly since the Society for Investigative Dermatology was founded in 1937, and it promises to continue growing rapidly. An aspect of this enterprise that receives less attention than the discovery process is the reduction to practice of new knowledge. Once new insights and approaches to manage disease are uncovered, this knowledge must be integrated into the practice of medicine. Successfully moving discovery into practice provides the deep satisfaction of knowing that one's research efforts have been worthwhile. Since the passage of the Bayh–Dole Act of 1980, which permitted universities to obtain patents and license inventions derived from government-funded research (Sampat, 2010), moving discovery into practice has also provided significant monetary benefits to investigators and their universities. If discoveries are transformative, the amounts of revenue generated can be very large. Because of this change in the law, patent grants to universities have increased from less than 300 a year in 1980 to more than 3,000, with US universities collectively earning almost $2 billion each year (Sampat, 2010). For departments lucky enough to have faculty that make such discoveries, these monies can create endowments that allow a department to be more supportive of cutting-edge science, take advantage of opportunities, or provide resources to support outstanding faculty. An excellent example of this is provided by the University of Pennsylvania—Albert Kligman did his seminal research on retinoic acid effects in skin while serving as a faculty member there, providing millions of dollars in royalties to the department to support its educational, research, and patient-care missions (Stanley, 2006).

Licensing of patent rights has also stimulated an increase in new university-associated small businesses; as many as three are created per university each year. More than two-thirds of these small companies were supported by universities taking equity positions in the company (AUTM Licensing Survey, http://www.autm.net/Surveys.htm). Royalty revenue can be big business for universities (although only about 10% actually realize large returns), so ensuring that their technology-transfer office is effective in supporting faculty inventors is important (Bulut and Moschini, 2009). Proper stewardship of faculty patents and licensing can provide a significant percentage of university revenue. In addition, the efficacy of university administrators, such as department chairs and the technology-transfer office, varies greatly from one institution to another. Table 1 lists the total research funding and license revenue for fiscal year 2009 at several universities, illustrating the diverse level of revenue that licensing provides to these institutions (AUTM Licensing Survey, http://www.autm.net/Surveys.htm).

For university researchers to realize the benefits of invention, the first step in the process is keeping an accurate and thorough record of the research being done. In its most stringent form, this process is called good laboratory practice (GLP). GLP is an approach to experimentation and documentation that entails systematic controls on research quality as well as managing the research process to ensure uniformity, consistency, reliability, and reproducibility of the data. The process is required for data that are to be presented to the US Food and Drug Administration for assessment of new drugs (Knight and Cree, 2011). In a pharmaceutical manufacturing environment, rigorous attention is paid to standards and maintenance of the laboratory equipment, test facility operation, and documentation of personnel training. The origin of materials; their quality, labeling, and storage; conduct of experiments to include all proper controls; and logs documenting these items are required. Key aspects of proper GLP documentation are summarized in Table 2.

In the cutting-edge research conducted at universities, not all aspects of GLP are required, but thorough documentation of laboratory work is requisite. Determination of inventorship

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can depend on defining the path of idea creation, so relevant discussions with others should also be documented, and corroborated in writing by those involved. It is especially important to document dates when discussions or experiments took place. The overall emphasis for documentation is that the researcher demonstrate diligence in the pursuit of discovery. Although data generated in the course of conducting scientific research do not necessarily become the subject of a patent's claims, data that are not directly part of the claims can be very important for the purpose of enabling the invention, and the documentation should be complete. Ultimately, the notebook is used to establish patentability, the date of invention, and inventorship. In academia, it should be made clear to all participants in the scientific process what their role is in the discovery. Students rotating through laboratories, graduate students, and postdoctoral fellows should clearly understand whether their research activities constitute participation in the inventive process. Providing technical assistance for research does not constitute a role in the inventive process. It is the responsibility of the principal investigator to ensure that everyone involved in the project understands this relationship. Additionally, because disclosure of inventions to the public prior to patent filing can invalidate protection in some markets, students contributing to patentable research may face a conflict between being able to present their work and allowing the work to be patented. Principal investigators must be clear with students about such issues at all times.

Once a discovery is made, the next step in the process is securing patent protection (Pressman, 2011). This step can be problematic because public disclosure can lead to loss of patent rights. The investigator must recognize the need for patent protection and file the patent application before any "enabling" disclosures are made to the general public. How does the patenting process work? At a university, the invention must first be disclosed to the appropriate institutional department, usually the technology transfer office. Once a decision is made to seek patent protection, an application is drafted by a patent attorney. A patent application consists of several required sections: a description of the field covered by the patent, a description of related art that the new patent seeks to improve on, and a description of how the new invention is an improvement over background art or overcomes problems with existing art. If there are drawings, the drawings are described in detail.

The application next provides a detailed description of the invention. For example, if a gene was discovered, the sequence is listed in the detailed description. If it is a new computed tomography imaging device, it will show how the X-ray source is applied to the patient and how the signals are collected and present the mathematics of reconstructing the image for interpretation. The preferred embodiment of the invention is then discussed. Inventions may be carried out in a variety of ways, but the inventor must describe the best way to make and/or use the invention, although other embodiments may also be described. The patent must describe the invention completely and in sufficient detail that the reader with ordinary skill in the field can understand how to make and/or use it. The heart of the patent application is a claim or list of claims that define the scope of protection that will be legally conferred if the patent is granted.

As an example, a very abbreviated set of claims from US Patent 7,888,392 is presented in Table 3 (http://patft.uspto.gov). A classic dermatologic invention, this patent describes an ointment containing a pharmaceutical agent that has an antipruritic effect in a vehicle with low skin irritancy and excellent storage stability. As this patent illustrates, claims are broken down into independent and dependent claims. Of the four listed, claims 1 and 2 are independent and claims 3 and 4 are dependent. Claim 1 teaches the formula for the ointment (together with reference to the diagram; not shown here), and claim 2 teaches the method of making the ointment. Claims 3 and 4 further describe aspects of claim 1; hence, they are dependent claims.

After the claims, the final portion of a patent application is a short (fewer than 150 words) abstract describing the invention. When the patent is issued, the abstract is placed on the front page, together with the patent number, date, and title. The inventors are then listed, and in cases in which the inventors have the duty to assign their rights to the invention to their institution, there is a listing for the assignee. There is also a list of patents and other publications that the Patent Office used as "prior art" during examination of the patent application. Prior art becomes important in patent litigation if validity of the patent comes into question.

US patent law was written into the US Constitution in paragraph 8, section 8, of Article 1 and went into effect upon its signing. George Washington signed the first patent issued in the United States,

Table 1. Royalty revenue at several major universities

Institution	Total research funding ($)	Royalty revenue ($)	Royalty revenue as a percentage of the total
California Institute of Technology	521,436,800	47,665,535	9.1
Case Western Reserve	332,661,000	16,281,957	4.9
Columbia	604,660,000	154,257,579	25
Ohio State University	716,461,278	1,711,719	2.4
University of North Carolina	666,871,589	3,063,947	4.5
University of Rochester	337,246,000	46,025,270	13.6
Stanford	733,266,108	65,054,187	8.9

Table 2. Key features of laboratory notebooks in good laboratory practice

Bound notebook—do not remove any pages.
Entries are in ink.
No erasure marks—strike through the item and initial to indicate unwanted entries.
Experiments to be dated, with title, statement of objective, and a *detailed* description of the experiment being conducted.
Evaluation, interpretation, and conclusions about experiments are included.
All figures are labeled and abbreviations are defined. If data are to be attached to the notebook, they are taped in, with date, time, and signature.
Experiments are included in chronological order, and failed experiments are also included.
Timely signature and date by a witness who is not a coinventor.

on 31 July 1790. It was a dermatological patent for an ingredient used in making soap, granted to Samuel Hopkins (Evans, 1919). The purpose of patenting an invention is to create incentive for a commercial entity to use its resources to develop that technology. The patent grants a limited monopoly to the patent holder for a finite time, potentially creating a strong business advantage. Without the benefit of this limited monopoly, businesses would not expend the time and expense to bring many products to market. After patent protection expires, the technology moves into the public domain and is available to all. Thus, a patent creates a favorable business advantage initially and subsequently stimulates science through disclosure of knowledge in the context of its advantageous use (Evans, 1919).

For a discovery to be patentable, it must be novel, have utility, and be nonobvious (Pressman, 2011). Novelty is something that the inventor demonstrates by showing that the invention is different from all prior art in the public domain. Generally, the utility of an invention is quite clear—for example, the wheel on an automobile holds up the car. The nonobviousness requirement is the most difficult to meet. Patent examiners peruse previous patents and other publications in the public domain and can reject an application by finding that the invention is a combination of existing concepts A, B, and C (i.e., something that anyone of ordinary skill could have created, even if no one else actually has). Such an application is therefore obvious based on the existing prior art, in combination. It is only when the inventor can successfully demonstrate novelty, utility, and nonobviousness that a patent will be granted.

Another important aspect of a patent's validity is the correct designation of inventorship (Slowinski and Zerby, 2008). Determination of inventorship relies heavily on correct documentation of the research supporting the patent application. The lineage of ideas and their ownership must be regularly documented during the research process for inventorship to be clear and uncontested. Unlike scientific publications, patent inventorship is legally defined. With publications, it is possible to have someone who edited a manuscript but did not directly contribute to it be listed as an author. This is not the case with patents. Moreover, if a patent does not list the correct inventorship (e.g., if it lists "inventors" who do not meet the legal definition), it can be invalidated. Conversely, if it does not list all the inventors who contributed to the invention, it can also be found invalid. This becomes especially important during patent litigation. Additionally, in the eyes of patent law, all inventors are equal, even if they actually contributed to only one dependent claim. Every inventor has the right to practice that invention and the right to keep others from practicing it.

Of course, effective practice of an invention means that some new medicine or machine must be produced and distributed by a competent commercial partner. The term used for permission to practice someone else's invention is called a license (or licensing agreement). Once it is clear that an invention can be developed into a useful device, therapy, or service, and it is determined that it would be commercially feasible to use resources for its development, companies may enter into licensing agreements with universities to acquire permission to practice the invention. Such agreements provide the opportunity to create a revenue stream for the inventor, their department, and the university. To assist faculty in implementing their patented discoveries, institutions set up offices that manage their intellectual property or hire outside entities (usually law firms) to manage their patent portfolios.

With the signing of the Leahy–Smith America Invents Act (H.R. 1249) on 16 September 2011, the US patent system was transformed from a "first-to-invent" system to a standard common in the rest of the world, where patent rights are granted to the first inventors to file their application.

Formerly, an inventor had a one-year grace period after public disclosure of an invention to file a patent application protecting it (Jackson, 1967). "Public disclosure" under the former law included printed publication, presentations, offers for sale, and certain public uses. The Leahy–Smith Act limits the activities allowed by the inventor under the one-year grace period to printed publications and public presentations. Fortunately, research applications to the National Institutes of Health are not considered public disclosures. Retaining the grace period for publications by inventors is an important consideration for academic researchers. In academics, we must publish our work to advance our careers as well as to advance science. The publication grace period under the new patent law, although more limited than before, still provides a marked distinction between US patent law and most other first-to-file systems. In many other countries, for patent rights to be preserved there must be absolute novelty. This means nothing can be in print, or otherwise available to the public, that enables one to practice the invention. Lack of

Table 3. Abbreviated set of claims from US Patent 7,888,392

1. An oleaginous ointment consisting of a compound represented by formula (I, shown in patent diagrams) and an oleaginous base, wherein the compound is dispersed but not dissolved in a solid or oily state; and wherein the compound is present in 0.000001% to 0.1% by weight; wherein the oleaginous base comprises a purified white petrolatum; and wherein the ointment is produced by adding a dispersing compound represented by formula (II) in the oleaginous base.
2. A method for producing an oleaginous ointment as described above comprising: (i) dispersing the compound represented by formula (I) in the oleaginous base in a solid or oily state to obtain a dispersion; (ii) adding the dispersion to the oleaginous base maintained at a temperature between 45 and 55 degrees C; and (iii) mixing the dispersion and the oleaginous base with stirring.
3. The ointment according to claim 1, wherein the oleaginous base is a white petrolatum which has been purified by removing impurities that are absorbable to silica gel.
4. The ointment according to claim 1, wherein the oleaginous base further comprises one or more selected from the group consisting of light liquid paraffin, liquid paraffin, paraffin, squalane, methylpolysiloxane, and gelated hydrocarbons.

attention to this requirement can have huge consequences—public disclosure through public presentation or publication can cause an inventor to lose the opportunity to protect his or her invention in many big markets. In the case of topical dermatologic products, even limited production or sales of the invention cannot occur if patent rights are to be secured.

How does a university office of technology transfer support faculty in the process of obtaining patents for their inventions and facilitating their licensing? Typically, once the office receives a disclosure, the commercial potential and the patentability are assessed (Miller *et al*., 2009). A prior art search is conducted because the inventor may be unaware that the invention has already been patented or otherwise disclosed. If there appears to be commercial viability and true novelty, the office will file a patent application to protect the invention. This process will also demand some time from the faculty member and must be done correctly for patent protection to be provided. It can be frustrating and complicated, but if successful, it is the key to translating research into practical, beneficial change in science and medicine. Department administrators must recognize the complexity and time constraints that accompany the pursuit of patent protection and create a culture in which faculty are supported in the process (Bercovitz and Feldmann, 2006). Clearly some institutions have been much more successful at this than others, as demonstrated in Table 1.

The technology-transfer office generally does not wait for the patent to be issued to begin marketing an invention; it can begin almost immediately. Universities establish standard policies and procedures to ensure that key aspects of the process move ahead correctly (Bercovitz and Feldmann, 2006). A nonconfidential disclosure of the novel technology is put up on the university's website and into repositories where individuals looking for new technologies know they will find useful information. One such repository is called Ibridge (http://www.ibridgenetwork.org), for "intellectual property bridge," where universities can make their technologies available to the public. Marketing inventions is now done largely through this method. Technology-transfer offices also are likely to do some targeted marketing to companies that have previously licensed university technologies when a similar technology arises (Miller *et al*., 2009).

When a company sees potential for a particular technology, it initiates communication with the technology-transfer office. The dialog begins between the university manager for the technology and the business development manager for the interested company. The discussion might require a confidential disclosure agreement to allow confidential information to be exchanged. Faculty are often surprised by the need for such arrangements, but they are in place to secure business opportunities for companies and to protect intellectual property. Working quickly and effectively to secure such documentation is important to a company as it assesses whether it wishes to enter into a partnership with an inventor at a university. The ease with which this process is conducted sets the tone of the relationship for many companies (Slowinski and Zerby, 2008; Sampat, 2010). Alternatively, if the technology is covered by an issued patent, the interested company may just look at the patent, satisfy itself that the invention will be useful from a business standpoint, and contact the technology transfer office to begin the licensing process. In either situation, the office will ask the company to provide a plan for commercializing the technology. The plan must demonstrate that the company has the necessary business acumen, marketing ability, resources, and development capability to move the faculty member's invention forward (Bercovitz and Feldmann, 2006).

Technology licensing agreements with established companies can result in significant income to a university. Typical components of a license agreement are execution royalties, minimum annual royalties, earned royalties, and milestone payments. Milestone payments are often based on events such as completion of the first prototype, approval by the Food and Drug Administration, or first commercial sale. Such payments can add up—for a recent license at the University of Rochester, the first payment was $1.2 million. Creating these agreements and assessing the business plans of licensees requires experience and an understanding of the marketplace in which the invention is to be sold. For faculty and the departments in which they work, a good technology-transfer office eliminates the headache of trying to move an invention through the maze of issues involved in patenting and marketing while creating revenue that is divided among the inventors, the department, and the university.

Some inventions are at such an early stage in development that they may not be of interest to a large,

established company. In such cases, the office can work with the inventor and his or her business partners to form a start-up company. Again, the support of administration for faculty creating start-up companies is an absolute requirement for success (Bercovitz and Feldmann, 2006). No department will benefit from revenue generated by a successful start-up without understanding the requirements for success in the endeavor and providing help to educate faculty about how to proceed. Start-ups are very time consuming and require conflict-of-interest discussions and disclosures to clarify the delineation between company effort and that of the faculty member. Transparency is the key to long-term success in such situations.

Although many faculty believe their invention may be appropriate for patent protection, only a portion of the research discoveries brought to the technology-transfer office actually end up being patented. Depending on the mix of patents (pharmacology versus devices) and the commitment of the institution to technology transfer, the rate at which a particular university licenses its patents varies. Another important caveat is that fewer than 10% of patents issued are ever made into products. Given that the research-to-patent-to-market process is so complex and difficult to navigate, and is far outside the training and expertise of faculty inventors, it is easy to see how so many useful inventions end up derailed. Supportive, visionary departmental and university leadership is necessary for achieving success. A technology-transfer office that is knowledgeable and aggressive in marketing inventions is also very valuable in obtaining returns from faculty inventions (Bercovitz and Feldmann, 2006). Royalty revenue is big business for universities, so they have a vested interest in ensuring that their technology-transfer office is effective in supporting faculty inventors. Departments that recognize talent for invention in their faculty, educate them in appropriate documentation methodology, and support them through the long process to success are well positioned to benefit from the opportunities that licensing and business start-ups present for enriching the intellectual, research, and patient-care environments in their departments. Ultimately, patients may be the biggest winners when universities commit the resources necessary to translate discovery into practice.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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